Biotech Health Sci. 2016 May; 3(2):e35914. doi: 10.17795/bhs-35914.

Published online 2016 May 29. **Review Article**

Kinesin-1 Traffic Control in Neuronal Highway

Masoud Rahmati[1,*]

[1]Department of Physical Education and Sport Sciences, Faculty of Literature and Humanities, Lorestan University, Khorramabad, IR Iran

[*]*Corresponding author*: Masoud Rahmati, Department of Physical Education and Sport Sciences, Faculty of Literature and Humanities, Lorestan University, Khorramabad, IR Iran. Tel: +98-9124525538, Fax: +98-4215393, E-mail: rahmati.mas@lu.ac.ir.

Received 2015 December 30; **Revised** 2016 April 11; **Accepted** 2016 April 23.

Abstract

Context: The current study aimed to review research articles concerning kinesin-1 traffic control in the neuronal highways
Evidence Acquisition: This review article compromised previous studies published since 1980 using PubMed, Google scholar, Embase, Medline, science direct and SID databases according to the keywords.
Results: Kinesin-1 often recognizes scaffold proteins or adaptor proteins and binds to cargo membrane proteins directly as part of a protein complex. Several kinases and microtubule associated proteins are identified in the regulation of motor-cargo unloading. The mechanisms by which kinesin-1 recognizes and binds to specific cargos, and how to unload cargo and determine the direction of transport, are now identified.
Conclusions: In summary, the current review article demonstrated that some proteins such as adaptors, Scaffolds, chaperons and microtubule associated proteins and some metabolites, hormones, protein kinases and exercise training can regulate kinesin-1 traffic control in neuronal highway. These findings open exciting new areas of kinesin-1 research.

Keywords: Kinesin-1, Scaffold Proteins, Adaptor Proteins, Neuronal Transport

1. Context

Molecular traffic in mammals in a fine designed neural system is dedicated to molecular motors. Basically, this traffic is done by dynein and kinesin superfamily proteins. These molecular motors use high polarized structure of neurons to perform their duty (1). Among neuronal cytoskeleton main elements, only microtubules and actin filaments play an important role in supplying neuronal elaborated tracks. Molecular motors ultimately use microtubules organization in a polarized array for targeted transport of substances (1, 2). Whereas axonal microtubules are uniformly organized with the plus end directed toward the axonal terminals and minus end directed toward the soma, but dendritic microtubular polarization is mixed in orientation. Mostly, kinesins and dynein motor proteins use this polarization for anterograde and retrograde transport of cargos, respectively (1). So far, 45 kinesin genes are recognized in mammals that constitute 15 kinesin super families. Moreover, depending on the location and position of the kinesins motor domain, all 15 kinesin super families can be grouped in to three types: M-kinesins are involved in microtubules depolymerization; N-kinesins are plus end-directed and C-kinesins are minus end-directed (2, 3).

2. Evidence Acquisition

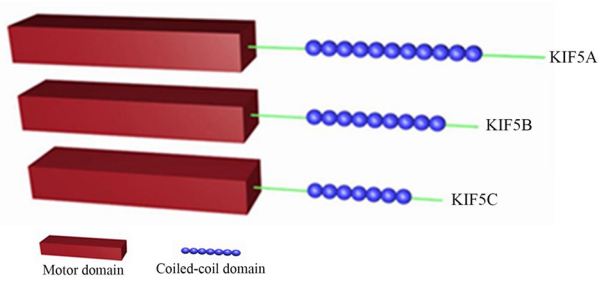
Kinesin-1 classified as an N-kinesin was the first identified kinesin motor protein in neuronal microtubule-based motility system and its roles and functions are well documented (4). In its structure, kinesin-1 has two heavy and two light chains. The motor role of kinesin-1 is dedicated to its two heavy chains known as KIF5 that use ATP as a fuel to generate the movement of kinesin-1 along with microtubules. Until now, three subtypes of KIF5 are discovered in mammals: KIF5A, KIF5B and KIF5C (1) (Figure 1). The N-terminal motor domain of each KIF5 can bind directly to microtubules and facilitate kinesin-1 directional motility. On the other hand, its C-terminal is involved in the association between KIF5 and kinesin light chains or direct attachment with intracellular cargo vesicles (1, 2). The current review focused on several important aspects of kinesin-1 regulation.

3. Results

3.1. Self-Regulation as an Intelligent Molecular Motor

To prevent futile ATP consumption/hydrolysis and heavy traffic in microtubular tracks in the neuronal cells kinesin-1 takes a folded shape as an auto-inhibition mechanism for the precise regulation in the presence of cargo, released from auto-inhibition and takes an active shape

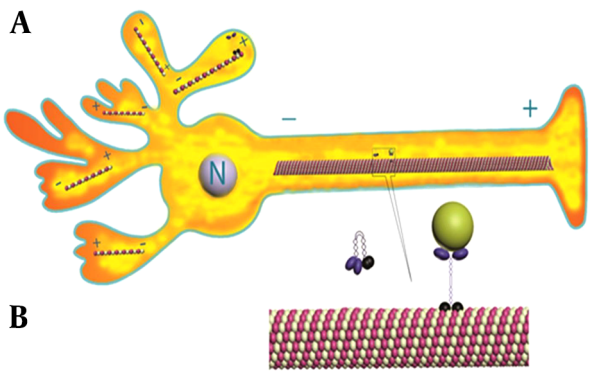
Figure 1. The Domain Structure of Knesin-1



Phylogenetic structures of kinesin-1 genes are classified into KIF5A, KIF5B, and KIF5C. In general, kinesin-1comprises a kinesin motor domain and a coiled-coil domain.

(5) (Figure 2). Moreover, microtubular stability and polarity are among the two most important aspects of axonal transport. Evidence shows that kinesin-1 can regulate microtubular stability and polarity. It was shown that in-vitro kinesin-1 directly binds to microtubules and mediates their gliding (6). Recent findings show that by gliding microtubules toward the plus-end-out in dendrites, kinesin-1 can regulate dendritic microtubular stability and polarity (7). Generally these findings indicate that kinesin-1 is involved in intracellular cargo traffic control by changing its shape in its rail road.

Figure 2. Intracellular Transport by Kinesin-1 Motor Protein in Neurons



A, unipolar microtubules in neuronal axons, and mixed directionality of microtubules is in proximal dendrites. In neuronal axons, microtubules are unipolar and the plus ends always point distally. Therefore, kinesin-1 as plus end-directed motors transports specific cargos to the cell periphery in axons. B, auto-inhibition mechanism for the kinesin-1 in the presence of cargo. In the absence of cargo, kinesin-1motors are auto-inhibited which assume a folded conformation that enables an inhibitory and direct motor-to-tail interaction (left). But, auto-inhibition state of kinesin-1 motors can be relieved by the interaction with cargoes (right).

3.2. Role of Microtubule Associated Proteins

Although the duty of axonal transport is dedicated to motor proteins, this event may be affected by microtubule associated proteins (MAPs) (8). MAPs are a distinct group of proteins thought to play an important role in mediating microtubule assembly and stability by binding to the tubulin. Among a large variety of identified MAPs, MAP2 as well as tau can inhibit the binding of kinesin-1 to microtubules and thereby lead to disrupted axonal transport (9). MAP4 is another MAP isoform that in contrast to MAP2 does not compete with kinesin-1 to bind to microtubules, but acts as roadblocks and can stop kinesin-1 motility by altering microtubular properties (10). Also, tau as a MAP is involved in the stabilization of microtubules. Evidence shows that excessive tau phosphorylation inhibits kinesin-1-driven axonal transport of vesicles, mitochondria, and endoplasmic reticulum attributed to the Alzheimer's disease pathology (11, 12). The plus end interacting protein (+TIP) EB1 as a MAP can increase microtubule stiffness and slow kinesin-1 motility (13).

Prion protein (PrP) is a misfolded form of natural proteins existing in cellular membranes of brain neurons and other types of cells and plays an important role in the pathogenesis of numerous neurodegenerative diseases. Hence, direct interaction with tubulin, PrP leads to its oligomerization/aggregation and finally inhibits microtubule assembly in-vitro and impairs kinesin-1 driven transport (14). Moreover, recent work in Drosophila S2 cells showed that ensconsin is an MAP kinesin-1 released from auto-inhibited state required for kinesin-1 organelle transport (15).

3.3. The Role of Adaptor Proteins

By integration of multiple signaling pathways, mammalian cells can response appropriately and specifically to external stimulus. Once cell surface receptors are stimulated, post-translational modifications such as phosphorylation leads to cellular signals initiation which require some modifications including specific protein binding to specific subcellular domains. In cell biology, adaptor proteins are an emerging class of proteins involved in all of the aforementioned processes (16). Due to the important role of kinesin-1 in neuronal signaling pathways, adaptor proteins are one of the major regulators of this motor protein.

Collapsin response of mediator protein-2 (CRMP2) is enriched in brain neurons that can regulate neuronal microtubule assembly. In addition to the growth cone dynamic (17) and neurite outgrowth regulation (18), CRMP2 also leads to kinesin-1-dependent tubulin transport in the developing neurons by binding to KLC1 (19). Also, caytaxin

is an adaptor protein that plays an important role in cerebellum function and its deficit leads to ataxia (20) and dystonia (21). Caytaxin can bind to KLC1 and modulate intracellular transport of specific cargoes such as mitochondria in hippocampus neurons (22).

Also, portrudine as an adaptor protein can facilitate kinesin-1 interaction with Rab-11, VAP-A, VAP-B, surf4, and RNT3 and protrudine-kinesin-1 complex contributes to the axonal anterograde vesicular transport of these proteins in mouse brain (23). The S100 protein family Ca^{2+}-binding proteins are in cytoplasm of different cells and are involved in multiple cell processes such as cell cycle progress and differentiation. It is shown that S100A2 and S100A6 in a Ca^{2+}-regulated fashion can bind to tetratricopeptide (TPR) domains of KLC. Moreover, S100A6 can inhibit KLC- (JNK)-interacting protein 1 (JIP-1) interaction (24). DAXX death related protein is one of the FAS ligand interacting proteins that can acts as a protein interaction modulator and activates JNK and apoptosis in different cell functions. Also, DAXX can interact with Glut-4 (25) and Glut-4 is one of the kinesin-1 cargoes transported along with microtubules (26). Recent evidence showed that DAXX, as an adaptor protein, interacts with KLC-TPR domain and plays an important role in cargo transport at adipose cell tissues (27).

Kidins220 (kinase D-interacting substrate of 220 k Da) is an integral membrane protein which exists in highly plastic areas of the adult brain neurons and plays an important role in developing the nervous system (28-30). Kidins220 can interact with KLC1 and facilitate kinesin-1-dependent transport linked to neurotrophin action (22). Moreover, Kidins220 can regulate neuronal polarity (31) by interaction with tubulin and MAPs. The 14-3-3 proteins are a family of proteins that participate in the regulation of a wide range of biological processes such as signal transduction, cell cycle, transcription, apoptosis, and neuronal development (32). These proteins can attach to phosphorylate Huntingtin-associated protein (1HAP1) and reduce KLC2-HAP1 interaction (33). Elongation protein zeta 1 (FEZ1) is another specific kinesin-1 adaptor protein that facilitates syntaxin 1 (syntaxin) and synaptotagmin (34) axonal transport. Although, RAN binding protein 2 (RANBP2) can approximately increase ATPase activity of KIF5B by 30 folds in the presence of ATP and microtubules, it induces unfolding and inactive shape of KIF5B (35) in the absence of microtubules.

3.4. The Role of Scaffold Proteins

Scaffold proteins are known as a regulator of many cellular signaling pathways that play an important role in signal transduction by interacting with multiple members of a signaling pathway. The role of c-jun NH2-terminal kinase (JNK)-interacting proteins (JIPs) JIP-1, JIP-2, JIP-3 and JIP-4, which are scaffolding proteins for the JNK signaling pathway in kinesin-1 regulation, are well documented (36). TPR domain of KLC can interact with JIP-1 (37), JIP-2, JIP3 (38), JIP-4 (39), JNK-associated leucine zipper protein (JLP) (40), Torsin A (41), HAP1 (42) and calsytenin-1 (43). Recent evidence show that JIP-1 cannot directly play a role in kinesin-1-cargo attachment and this event is dependent on the interaction between JIP-3 and PTB (phosphotyrosine binding) domains of kinesin-1 (44). Also, JIP-1 plays an important role in the attachment of apolipoprotein E receptor 2 (APOER2) cargos with kinesin-1 (36), Similar to other JIPs, JLP can assemble JNK signaling (45) through upstream kinases such as MKK4 and MEKK3.

3.5. Role of Chaperon Proteins

Environmental stress leads the cells to change their expression program, which almost all of these genes include, that encode heat shock proteins (Hsps). These proteins act as molecular chaperones and play an important role in a wide range of cellular processes including preventing from unwanted interactions between unfolded polypeptides during their synthesis or transport, irreversible aggregation of proteins, and refolding denatured proteins (46). According to their molecular weights, Hsps family can be divided and Hsp40, Hsp60, Hsp70, Hsp90, and Hsp100 are the most important Hsps until today (47).

It was found that among different chaperone proteins, both Hsp70 and Hsp110 interact with tubulin subunits. Moreover, KLC1 can attach to Hsp70 and Hsp110 (48) and these findings shows that chaperone proteins are involved in neuronal transport. For better understanding the role of Hsp70, it was shown that it plays an important role in axonal transport of synaptic vesicles by releasing kinesin-1 from cargo in specific subcellular domains (49). Also, Hsp70 can partially rescue a vesicle transport defect produced by an ALS disease model, while Hsp110 completely rescued this problem (50).

3.6. Regulation Depending on Different Gene Expression Patterns

Variety of kinesin in different tissues of mammalian, especially in neuronal cells, represents their different responsibilities in any type of cells. Authors previously demonstrated that diabetes increases KIF5B mRNA and protein levels and exercise endurance can modify it in spinal cord (51). Silverman et al. investigated the gene expression of twenty kinesins super family members in embryonic and adult hippocampal tissue cultures. Their results showed that kinesin-13, involved in microtubule depolymerization, is expressed in hippocampal neurons at high levels and kinesin-9 and -14 family members, which

their functions are not elucidated yet, are expressed at moderate-to-high levels. While in embryonic hippocampus 10 mitotic kinesins were expressed at moderate levels, in mature cultures and the adult hippocampus their expression patterns were at very low levels (52). In agreement with this finding, Takemura et al., showed that after sciatic crush injury, kinesin-1 and KIF1B gene expression levels were 50% - 80% of the control in dorsal root ganglion neuron (DRG) (53). Collectively, these findings suggest that according to the diverse functions within a single type of neuron, expression patterns of kinesins super family members could be changed and they can adapt to the cell needs.

3.7. Role of Metabolites

Kinesin super families can move along microtubules and transport their cargoes by generating about 6 pN of force at a speed of about 1 μm s^{-1} with about 50% efficiency from hydrolysis of ATP (54). After ATP hydrolysis at KHC, Pi is released in one head of kinesin and after that in the other head ADP could be released. This is exactly the mechanism to explain the hand-over-hand pattern for kinesin movement along microtubules (55). Therefore, it seems that ATP hydrolysis rate and amount can affect kinesin function and movement. Evidence showed that ATP low and high concentrations lead to weak and strong force production of kinesin, respectively (56). On the other hand, while kinesin run length is independent of ATP concentration, elevated ADP concentration decreases both velocity and run lengths (57). These findings suggest that kinesin movement properties are depended on the ATP concentration and hydrolysis. Neurons are very sensitive to pH > 7.5; therefore, kinesin-cargo interaction may have a pH-dependent manner. Kinesin-dependent motility and transport increased upon acidification in neuronal cells (58). Elevated temperature and MG^{2+}/ATP ratio are other metabolites-dependent speed (59).

3.8. Role of Hormones

The human pro-adrenomedullin protein directs post-translational modifications and finally leads to production of two biologically active peptides: adrenomedullin (AM) and pro-adrenomedullin N-terminal 20-peptide (PAMP) (60). These peptides are known as a regulator of many physiological processes including vasodilatation; bronchodilatation; hormone secretion regulation; antimicrobial activities; and modulation of cell growth, apoptosis, migration, and angiogenesis (61). In addition to their extracellular roles, they can interact with the microtubules in especial cell types (62). While AM can bind to MAPs, PAMP directly interacts with tubulin and kinesin-1 and postpones tubulin polymerization (62). Recent evidence shows, in-vitro and in-vivo, that PAMP can directly interact with kinesin-1 and increase its velocity along microtubules and ATPase activities (63). The current study suggests that PAMP is a first peptide that can regulate kinesin-1 motility.

3.9. The Role of Protein Kinases

Protein kinases participate in a variety of functions, including signal transduction, regulation of ion channels and neurotransmitter release, control of cell growth and differentiation, and changes in cell morphology and gene expression (64, 65). Protein kinase A (PKA)-dependent phosphorylation of KIF5-KLC complex, inhibits kinesin-1 from binding to synaptic vesicles (66). Also, glycogen synthase kinase 3 inhibits the interaction between KIF5-KLC complexes and membrane organelles (67) by phosphorylation of KLC in the same manner. In addition, as a protein kinase JNK can phosphorylate KIF5 motors (37, 68) and thereby leads to weak motor–microtubule associations (40). Moreover, abnormal activation of JNK signaling pathway disturbs axonal transport (36) by detachment of kinesin-cargo associations. Also, protein kinases can regulate microtubular stability and polarity. In this regard, glycogen synthases kinase 3β (GSK3β)-induced phosphorylation disturb microtubular stability (69). In addition, GSK3β can phosphorylate tau, MAP2, MAP1B, CRMP2, APC and axin (47, 70). Cyclin-dependent kinase (Cdk5) is another protein kinase that can phosphorylate tau, regulate microtubular stability and kinesin-1 localization (71). In addition, GSK3β can directly phosphorylate the KlC subunit of a kinesin-1 motor and decrease its association with membrane-bound organelles (5). Authors previously showed that decreased activity and tight ligation of the L5 spinal nerve in neuropathic pain rats cause muscle decrease and increase in CDK5 and GSK-3β mRNA levels, respectively and these changes are followed by pain-related disorders and soleus muscle atrophy (64).

3.10. The Role of Cargoes

Members of the kinesin-1 family drive the transport of a wide range of cargos along the axon including vesicles, organelles, proteins and RNA particles. The light chains contain tetratricopeptide repeat protein-interaction motifs (TPRs), which can dock onto adaptors or cargo receptors, linking kinesin-1 to the cargo to be transported (1). It is possible that the cargoes transported by kinesin regulate kinesin-mediated transport. Alcadeinα (Alcα) is an evolutionarily conserved type I membrane protein expressed in neurons. Alcα can be transported by kinesin-1 with slower speed than ATP containing vesicles. Moreover, Alcα can bind vesicles to kinesin-1 and regulate kinesin-cargo interaction. Also, Alcα can activate kinesin-1 or block transport

of APP-containing vesicles (72) by direct interaction with KLC. Coordination of kinesin-1 needs to be highly regulated. Many lines of evidence support the view that kinesin-1-mediated transport is modulated by phosphorylation of the motor proteins or the cargoes. Kinesin phosphorylation on serine residues correlates with cargo binding in cultured cells, whereas the release of kinesin from vesicles correlates with the phosphorylation of KLC by glycogen synthase kinase 3β (GSK3β), which acts as an inhibitor of fast anterograde transport (1, 2, 64, 73). In addition, hyperphosphorylation of tau by GSK3β or CDK5 reduces its affinity for microtubules and its ability to promote microtubule assembly and modulates its ability to stabilize microtubules into organized arrays in-vitro (2, 74). These findings suggest that many aspects of kinesin-1 regulation may depend on the interaction between motor proteins and cargoes.

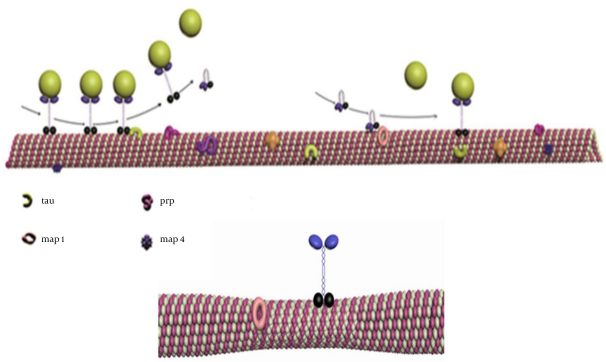
3.11. The kinesin-1 and Neurodegenerative Diseases

Maintenance and function of neurons are dependent on the intracellular transport of organelles along the axons. Basically, having a good synaptic function and mitochondria for local energy requirements in neurons are dedicated to molecular motor proteins that anterogradely transport cargoes (1). Neurodegenerative diseases are characterized by significant defects in synaptic function and dying-back degeneration of axons (1, 75). Accordingly, alterations in fast axonal transport are documented in the Alzheimer, Parkinson And Huntington diseases and amyotrophic lateral sclerosis (1, 2). These diseases are associated with mutations/dysfunctions in molecular motor proteins or alterations in the activity of specific protein kinases implicated in regulation of these motor proteins' function (2, 68). For example, mutation in KIF5A results in a hereditary form of spastic paraplegia, a disease characterized by progressive dysfunction and degeneration of upper motor neurons (76). Moreover, kinesin mutations are caused by Charcot-Marie-Tooth (CMT) disease (77). In agreement with these studies, authors previously showed that diabetic neuropathy state changed neuronal kinesin-1 motor protein and endurance exercise training modified this change (51). Generally, it can be noticed that molecular motor proteins and their regulator seem to be the target of neurodegenerative diseases.

3.12. Kinesin-1 and Exercise Training

Previous studies showed that treadmill exercise training can improve peripheral nervous tissue regeneration after nerve injury and increases axonal regeneration after sciatic nerve transection (78, 79). Exercise training is an interesting model which increases activation of sensory and motor neurons, axonal transport of proteins, and synaptic remodeling (51, 79). Authors previously demonstrated that diabetic neuropathy changes spinal cord KIF5B and SYD mRNA and sciatic nerves KIF5B content and exercise training modifies it, which may be attributable to the training-induced decreased hyperglycemia. These studies proved that exercise training increases the quantity of axonal proteins and axonal transport. Moreover, the results showed that exercise training, as a neuroprotective strategy, can increase kinesin-1 levels in lumbar sensory and motor neurons. The researches in the field of axonal transport impairments in neurodegenerative diseases may be supportive of cargo and driver theory (51). This theory explains that in neurodegenerative diseases, down-regulation of neurotrophic factors and other proteins essential for neuronal survival. Also, impairment in motor proteins transports these cargoes actively (51). Another important issue related to this theory refers to the modifying role of exercise. However, there are other related points which should be explained by future studies.

Figure 3. The Role of MAPs in Kinesin-1 Regulation

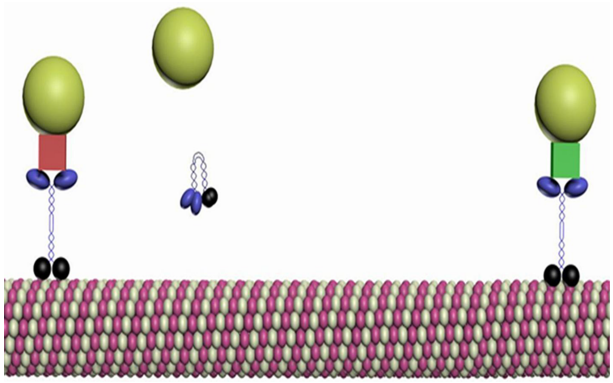


At the point of departure, motor-cargo complexes should navigate microtubule tracks. MAPs bind to the outer surface of microtubules and can cause decreased attachment and/or increased detachment of kinesin-1 motors and/or vesicles. Transport of kinesin-1-driven can be influenced by some MAPs such as tau, MAP1, MAP4, ensconsin, and PrP (top panel, left part). This event can be negatively influenced by the tau and MAP2 which can inhibit the binding of kinesin-1 to microtubules and thereby lead to disrupted axonal transport. In addition, MAP4 acts as road blocks and can stop kinesin-1 motility by altering microtubular properties. In contrast, ensconsin released kinesin-1 from auto-inhibited state (top panel, right part). Moreover, PrP leads to oligomerization/aggregation of tubulin and finally inhibits a microtubule assembly. The down part shows that some MAPs such as EB1 can increase microtubule stiffness and slow kinesin-1 motility.

4. Conclusions

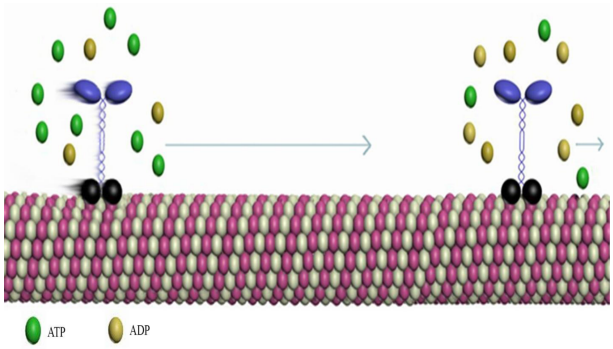
The role of kinesin-1 in the development of axonal transport is well established, while the knowledge of involved regulatory mechanisms is rapidly growing. Future studies are required to elucidate how spatial information

Figure 4. Adaptor Proteins and Kinesin-1 Transport



Adaptor proteins are needed to attach cargo to kinesin-1. Auto-inhibition of kinesin-1 motors can be relieved by the interaction with adaptor proteins that release the restraints of microtubule binding and processive motility.

Figure 5. ATP and ADP Concentration in Kinesin-1 Regulation



High concentrations of ATP lead to strong force production of kinesin. On the other hand, high concentrations of ADP lead to weak force production of kinesin.

inside cells and signals outside cells regulate kinesin-1 and address what signals control the association and dissociation of kinesin-1 and cargos, thereby controlling neuronal transport. Furthermore, Future studies will reveal how kinesin-1 recognizes cargos, scaffold and adaptor proteins. Better understanding of these pathways would help improve the preventive, predictive, and therapeutic interventions in neurodegenerative diseases.

Acknowledgments

Author would like to acknowledge his gratitude to Dr. Fatemeh Azad for her endless supports.

References

1. Hirokawa N, Noda Y, Tanaka Y, Niwa S. Kinesin superfamily motor proteins and intracellular transport. *Nat Rev Mol Cell Biol.* 2009;**10**(10):682–96. doi: 10.1038/nrm2774. [PubMed: 19773780].
2. Millecamps S, Julien JP. Axonal transport deficits and neurodegenerative diseases. *Nat Rev Neurosci.* 2013;**14**(3):161–76. doi: 10.1038/nrn3380. [PubMed: 23361386].
3. Hirokawa N, Noda Y. Intracellular transport and kinesin superfamily proteins, KIFs: structure, function, and dynamics. *Physiol Rev.* 2008;**88**(3):1089–118. doi: 10.1152/physrev.00023.2007. [PubMed: 18626067].
4. Vale RD, Reese TS, Sheetz MP. Identification of a novel force-generating protein, kinesin, involved in microtubule-based motility. *Cell.* 1985;**42**(1):39–50. [PubMed: 3926325].
5. Verhey KJ, Hammond JW. Traffic control: regulation of kinesin motors. *Nat Rev Mol Cell Biol.* 2009;**10**(11):765–77. doi: 10.1038/nrm2782. [PubMed: 19851335].
6. Seeger MA, Rice SE. Microtubule-associated protein-like binding of the kinesin-1 tail to microtubules. *J Biol Chem.* 2010;**285**(11):8155–62. doi: 10.1074/jbc.M109.068247. [PubMed: 20071331].
7. Yan J, Chao DL, Toba S, Koyasako K, Yasunaga T, Hirotsune S, et al. Kinesin-1 regulates dendrite microtubule polarity in Caenorhabditis elegans. *Elife.* 2013;**2**:e00133. doi: 10.7554/eLife.00133. [PubMed: 23482306].
8. Lawrence CJ, Dawe RK, Christie KR, Cleveland DW, Dawson SC, Endow SA, et al. A standardized kinesin nomenclature. *J Cell Biol.* 2004;**167**(1):19–22. doi: 10.1083/jcb.200408113. [PubMed: 15479732].
9. Hagiwara H, Yorifuji H, Sato-Yoshitake R, Hirokawa N. Competition between motor molecules (kinesin and cytoplasmic dynein) and fibrous microtubule-associated proteins in binding to microtubules. *J Biol Chem.* 1994;**269**(5):3581–9. [PubMed: 8106402].
10. Tokuraku K, Noguchi TQ, Nishie M, Matsushima K, Kotani S. An isoform of microtubule-associated protein 4 inhibits kinesin-driven microtubule gliding. *J Biochem.* 2007;**141**(4):585–91. doi: 10.1093/jb/mvm063. [PubMed: 17317690].
11. Ebneth A, Godemann R, Stamer K, Illenberger S, Trinczek B, Mandelkow E. Overexpression of tau protein inhibits kinesin-dependent trafficking of vesicles, mitochondria, and endoplasmic reticulum: implications for Alzheimer's disease. *J Cell Biol.* 1998;**143**(3):777–94. [PubMed: 9813097].
12. Obulesu M, Venu R, Somashekhar R. Tau mediated neurodegeneration: an insight into Alzheimer's disease pathology. *Neurochem Res.* 2011;**36**(8):1329–35. doi: 10.1007/s11064-011-0475-5. [PubMed: 21509508].
13. Lopez BJ, Valentine MT. The microtubule-associated protein eb1 affects both kinesin translocation and microtubule stiffness in vitro. *Biophys J.* 2013;**104**(2):144a. doi: 10.1016/j.bpj.2012.11.816.
14. Nieznanska H, Dudek E, Zajkowski T, Szczesna E, Kasprzak AA, Nieznanski K. Prion protein impairs kinesin-driven transport. *Biochem Biophys Res Commun.* 2012;**425**(4):788–93. doi: 10.1016/j.bbrc.2012.07.153. [PubMed: 22885185].
15. Barlan K, Lu W, Gelfand VI. The microtubule-binding protein ensconsin is an essential cofactor of kinesin-1. *Curr Biol.* 2013;**23**(4):317–22. doi: 10.1016/j.cub.2013.01.008. [PubMed: 23394833].
16. Schechtman D, Mochly-Rosen D. Adaptor proteins in protein kinase C-mediated signal transduction. *Oncogene.* 2001;**20**(44):6339–47. doi: 10.1038/sj.onc.1204778. [PubMed: 11607837].
17. Uchida Y, Ohshima T, Sasaki Y, Suzuki H, Yanai S, Yamashita N, et al. Semaphorin3A signalling is mediated via sequential Cdk5 and GSK3beta phosphorylation of CRMP2: implication of common phosphorylating mechanism underlying axon guidance and Alzheimer's disease. *Genes Cells.* 2005;**10**(2):165–79. doi: 10.1111/j.1365-2443.2005.00827.x. [PubMed: 15676027].
18. Cole AR, Knebel A, Morrice NA, Robertson LA, Irving AJ, Connolly CN, et al. GSK-3 phosphorylation of the Alzheimer epitope within collapsin response mediator proteins regulates axon elongation in primary neurons. *J Biol Chem.* 2004;**279**(48):50176–80. doi: 10.1074/jbc.C400412200. [PubMed: 15466863].

19. Cole AR, Noble W, van Aalten L, Plattner F, Meimaridou R, Hogan D, et al. Collapsin response mediator protein-2 hyperphosphorylation is an early event in Alzheimer's disease progression. *J Neurochem.* 2007;**103**(3):1132–44. doi: 10.1111/j.1471-4159.2007.04829.x. [PubMed: 17683481].
20. Gilbert N, Bomar JM, Burmeister M, Moran JV. Characterization of a mutagenic B1 retrotransposon insertion in the jittery mouse. *Hum Mutat.* 2004;**24**(1):9–13. doi: 10.1002/humu.20060. [PubMed: 15221784].
21. Xiao J, Ledoux MS. Caytaxin deficiency causes generalized dystonia in rats. *Brain Res Mol Brain Res.* 2005;**141**(2):181–92. doi: 10.1016/j.molbrainres.2005.09.009. [PubMed: 16246457].
22. Aoyama T, Hata S, Nakao T, Tanigawa Y, Oka C, Kawaichi M. Cayman ataxia protein caytaxin is transported by kinesin along neurites through binding to kinesin light chains. *J Cell Sci.* 2009;**122**(Pt 22):4177–85. doi: 10.1242/jcs.048579. [PubMed: 19861499].
23. Matsuzaki F, Shirane M, Matsumoto M, Nakayama KI. Protrudin serves as an adaptor molecule that connects KIF5 and its cargoes in vesicular transport during process formation. *Mol Biol Cell.* 2011;**22**(23):4602–20. doi: 10.1091/mbc.E11-01-0068. [PubMed: 21976701].
24. Shimamoto S, Takata M, Tokuda M, Oohira F, Tokumitsu H, Kobayashi R. Interactions of S100A2 and S100A6 with the tetratricopeptide repeat proteins, Hsp90/Hsp70-organizing protein and kinesin light chain. *J Biol Chem.* 2008;**283**(42):28246–58. doi: 10.1074/jbc.M801473200. [PubMed: 18669640].
25. Lalioti VS, Vergarajauregui S, Pulido D, Sandoval IV. The insulin-sensitive glucose transporter, GLUT4, interacts physically with Daxx. Two proteins with capacity to bind Ubc9 and conjugated to SUMO1. *J Biol Chem.* 2002;**277**(22):19783–91. doi: 10.1074/jbc.M110294200. [PubMed: 11842083].
26. Imamura T, Huang J, Usui I, Satoh H, Bever J, Olefsky JM. Insulin-induced GLUT4 translocation involves protein kinase C-lambda-mediated functional coupling between Rab4 and the motor protein kinesin. *Mol Cell Biol.* 2003;**23**(14):4892–900. [PubMed: 12832475].
27. Lalioti VS, Vergarajauregui S, Tsuchiya Y, Hernandez-Tiedra S, Sandoval IV. Daxx functions as a scaffold of a protein assembly constituted by GLUT4, JNK1 and KIF5B. *J Cell Physiol.* 2009;**218**(2):416–26. doi: 10.1002/jcp.21614. [PubMed: 18932217].
28. Cabrera-Poch N, Sanchez-Ruiloba L, Rodriguez-Martinez M, Iglesias T. Lipid raft disruption triggers protein kinase C and Src-dependent protein kinase D activation and Kidins220 phosphorylation in neuronal cells. *J Biol Chem.* 2004;**279**(27):28592–602. doi: 10.1074/jbc.M312242200. [PubMed: 15096499].
29. Iglesias T, Cabrera-Poch N, Mitchell MP, Naven TJ, Rozengurt E, Schiavo G. Identification and cloning of Kidins220, a novel neuronal substrate of protein kinase D. *J Biol Chem.* 2000;**275**(51):40048–56. doi: 10.1074/jbc.M005261200. [PubMed: 10998417].
30. Kong H, Boulter J, Weber JL, Lai C, Chao MV. An evolutionarily conserved transmembrane protein that is a novel downstream target of neurotrophin and ephrin receptors. *J Neurosci.* 2001;**21**(1):176–85. [PubMed: 11150334].
31. Higuero AM, Sanchez-Ruiloba L, Doglio LE, Portillo F, Abad-Rodriguez J, Dotti CG, et al. Kidins220/ARMS modulates the activity of microtubule-regulating proteins and controls neuronal polarity and development. *J Biol Chem.* 2010;**285**(2):1343–57. doi: 10.1074/jbc.M109.024703. [PubMed: 19903810].
32. Tzivion G, Avruch J. 14-3-3 proteins: active cofactors in cellular regulation by serine/threonine phosphorylation. *J Biol Chem.* 2002;**277**(5):3061–4. doi: 10.1074/jbc.R100059200. [PubMed: 11709560].
33. Rong J, Li S, Sheng G, Wu M, Coblitz B, Li M, et al. 14-3-3 protein interacts with Huntingtin-associated protein 1 and regulates its trafficking. *J Biol Chem.* 2007;**282**(7):4748–56. doi: 10.1074/jbc.M609057200. [PubMed: 17166838].
34. Toda H, Mochizuki H, Flores R3, Josowitz R, Krasieva TB, Lamorte VJ, et al. UNC-51/ATG1 kinase regulates axonal transport by mediating motor-cargo assembly. *Genes Dev.* 2008;**22**(23):3292–307. doi: 10.1101/gad.1734608. [PubMed: 19056884].
35. Cho KI, Yi H, Desai R, Hand AR, Haas AL, Ferreira PA. RANBP2 is an allosteric activator of the conventional kinesin-1 motor protein, KIF5B, in a minimal cell-free system. *EMBO Rep.* 2009;**10**(5):480–6. doi: 10.1038/embor.2009.29. [PubMed: 19305391].
36. Horiuchi D, Collins CA, Bhat P, Barkus RV, Diantonio A, Saxton WM. Control of a kinesin-cargo linkage mechanism by JNK pathway kinases. *Curr Biol.* 2007;**17**(15):1313–7. doi: 10.1016/j.cub.2007.06.062. [PubMed: 17658258].
37. Stagi M, Gorlovoy P, Larionov S, Takahashi K, Neumann H. Unloading kinesin transported cargoes from the tubulin track via the inflammatory c-Jun N-terminal kinase pathway. *FASEB J.* 2006;**20**(14):2573–5. doi: 10.1096/fj.06-6679fje. [PubMed: 17068110].
38. Verhey KJ, Meyer D, Deehan R, Blenis J, Schnapp BJ, Rapoport TA, et al. Cargo of kinesin identified as JIP scaffolding proteins and associated signaling molecules. *J Cell Biol.* 2001;**152**(5):959–70. [PubMed: 11238452].
39. Kelkar N, Standen CL, Davis RJ. Role of the JIP4 scaffold protein in the regulation of mitogen-activated protein kinase signaling pathways. *Mol Cell Biol.* 2005;**25**(7):2733–43. doi: 10.1128/MCB.25.7.2733-2743.2005. [PubMed: 15767678].
40. Nguyen Q, Lee CM, Le A, Reddy EP. JLP associates with kinesin light chain 1 through a novel leucine zipper-like domain. *J Biol Chem.* 2005;**280**(34):30185–91. doi: 10.1074/jbc.M505499200. [PubMed: 15987681].
41. Kamm C, Boston H, Hewett J, Wilbur J, Corey DP, Hanson PI, et al. The early onset dystonia protein torsinA interacts with kinesin light chain 1. *J Biol Chem.* 2004;**279**(19):19882–92. doi: 10.1074/jbc.M401332200. [PubMed: 14970196].
42. McGuire JR, Rong J, Li SH, Li XJ. Interaction of Huntingtin-associated protein-1 with kinesin light chain: implications in intracellular trafficking in neurons. *J Biol Chem.* 2006;**281**(6):3552–9. doi: 10.1074/jbc.M509806200. [PubMed: 16339760].
43. Vagnoni A, Rodriguez L, Manser C, De Vos KJ, Miller CC. Phosphorylation of kinesin light chain 1 at serine 460 modulates binding and trafficking of calsyntenin-1. *J Cell Sci.* 2011;**124**(Pt 7):1032–42. doi: 10.1242/jcs.075168. [PubMed: 21385839].
44. Satake T, Otsuki K, Banba Y, Suenaga J, Hirano H, Yamanaka Y, et al. The interaction of Kinesin-1 with its adaptor protein JIP1 can be regulated via proteins binding to the JIP1-PTB domain. *BMC Cell Biol.* 2013;**14**:12. doi: 10.1186/1471-2121-14-12. [PubMed: 23496950].
45. Lee CM, Onesime D, Reddy CD, Dhanasekaran N, Reddy EP. JLP: A scaffolding protein that tethers JNK/p38MAPK signaling modules and transcription factors. *Proc Natl Acad Sci U S A.* 2002;**99**(22):14189–94. doi: 10.1073/pnas.232310199. [PubMed: 12391307].
46. Meimaridou E, Gooljar SB, Chapple JP. From hatching to dispatching: the multiple cellular roles of the Hsp70 molecular chaperone machinery. *J Mol Endocrinol.* 2009;**42**(1):1–9. doi: 10.1677/JME-08-0116. [PubMed: 18852216].
47. Makhnevych T, Houry WA. The control of spindle length by Hsp70 and Hsp110 molecular chaperones. *FEBS Lett.* 2013;**587**(8):1067–72. doi: 10.1016/j.febslet.2013.02.018. [PubMed: 23434584].
48. Scheufler C, Brinker A, Bourenkov G, Pegoraro S, Moroder L, Bartunik H, et al. Structure of TPR domain-peptide complexes: critical elements in the assembly of the Hsp70-Hsp90 multichaperone machine. *Cell.* 2000;**101**(2):199–210. doi: 10.1016/S0092-8674(00)80830-2. [PubMed: 10786835].
49. Tsai MY, Morfini G, Szebenyi G, Brady ST. Release of kinesin from vesicles by hsc70 and regulation of fast axonal transport. *Mol Biol Cell.* 2000;**11**(6):2161–73. [PubMed: 10848636].
50. Song Y, Nagy M, Ni W, Tyagi NK, Fenton WA, Lopez-Giraldez F, et al. Molecular chaperone Hsp110 rescues a vesicle transport defect produced by an ALS-associated mutant SOD1 protein in squid axoplasm. *Proc Natl Acad Sci U S A.* 2013;**110**(14):5428–33. doi:

10.1073/pnas.1303279110. [PubMed: 23509252].
51. Rahmati M, Gharakhanlou R, Movahedin M, Mowla SJ, Khazani A, Fouladvand M, et al. Treadmill training modifies KIF5B motor protein in the STZ-induced diabetic rat spinal cord and sciatic nerve. *Arch Iran Med.* 2015;**18**(2):94–101. [PubMed: 25644797].
52. Silverman MA, Kaech S, Ramser EM, Lu X, Lasarev MR, Nagalla S, et al. Expression of kinesin superfamily genes in cultured hippocampal neurons. *Cytoskeleton (Hoboken).* 2010;**67**(12):784–95. doi: 10.1002/cm.20487. [PubMed: 20862690].
53. Takemura R, Nakata T, Okada Y, Yamazaki H, Zhang Z, Hirokawa N. mRNA expression of KIF1A, KIF1B, KIF2, KIF3A, KIF3B, KIF4, KIF5, and cytoplasmic dynein during axonal regeneration. *J Neurosci.* 1996;**16**(1):31–5. [PubMed: 8613797].
54. Kim T, Meyhofer E, Hasselbrink EF. Biomolecular motor-driven microtubule translocation in the presence of shear flow: modeling microtubule deflection due to shear. *Biomed Microdevices.* 2007;**9**(4):501–11. doi: 10.1007/s10544-007-9057-3. [PubMed: 17522979].
55. Schief WR, Clark RH, Crevenna AH, Howard J. Inhibition of kinesin motility by ADP and phosphate supports a hand-over-hand mechanism. *Proc Natl Acad Sci U S A.* 2004;**101**(5):1183–8. doi: 10.1073/pnas.0304369101. [PubMed: 14734813].
56. Schnitzer MJ, Visscher K, Block SM. Force production by single kinesin motors. *Nat Cell Biol.* 2000;**2**(10):718–23. doi: 10.1038/35036345. [PubMed: 11025662].
57. Yajima J, Alonso MC, Cross RA, Toyoshima YY. Direct long-term observation of kinesin processivity at low load. *Curr Biol.* 2002;**12**(4):301–6. [PubMed: 11864570].
58. Sheetz MP, Yu H. Regulation of kinesin and cytoplasmic dynein-driven organelle motility. Seminars in Cell and Developmental Biology. Elsevier; .
59. Bohm KJ, Stracke R, Unger E. Speeding up kinesin-driven microtubule gliding in vitro by variation of cofactor composition and physicochemical parameters. *Cell Biol Int.* 2000;**24**(6):335–41. doi: 10.1006/cbir.1999.0515. [PubMed: 10860568].
60. Kitamura K, Sakata J, Kangawa K, Kojima M, Matsuo H, Eto T. Cloning and characterization of cDNA encoding a precursor for human adrenomedullin. *Biochem Biophys Res Commun.* 1993;**194**(2):720–5. doi: 10.1006/bbrc.1993.1881. [PubMed: 7688224].
61. Lopez J, Martinez A. Cell and molecular biology of the multifunctional peptide, adrenomedullin. *Int Rev Cytol.* 2002;**221**:1–92. [PubMed: 12455746].
62. Sackett DL, Ozbun L, Zudaire E, Wessner L, Chirgwin JM, Cuttitta F, et al. Intracellular proadrenomedullin-derived peptides decorate the microtubules and contribute to cytoskeleton function. *Endocrinology.* 2008;**149**(6):2888–98. doi: 10.1210/en.2007-1763. [PubMed: 18325988].
63. Larrayoz IM, Martinez A. Proadrenomedullin N-terminal 20 peptide increases kinesin's velocity both in vitro and in vivo. *Endocrinology.* 2012;**153**(4):1734–42. doi: 10.1210/en.2011-1685. [PubMed: 22334720].
64. Rahmati M, Taherabadi SJ, Mehrabi M. Decreased Activity in Neuropathic Pain Form and Gene Expression of Cyclin-Dependent Kinase5 and Glycogen Synthase Kinase-3 Beta in Soleus Muscle of Wistar Male Rats. *Iran Red Crescent Med J.* 2015;**17**(6):e23324. doi: 10.5812/ircmj.23324. [PubMed: 26290750].
65. Salcedo-Tello P, Ortiz-Matamoros A, Arias C. GSK3 Function in the Brain during Development, Neuronal Plasticity, and Neurodegeneration. *Int J Alzheimers Dis.* 2011;**2011**:189728. doi: 10.4061/2011/189728. [PubMed: 21660241].
66. Sato-Yoshitake R, Yorifuji H, Inagaki M, Hirokawa N. The phosphorylation of kinesin regulates its binding to synaptic vesicles. *J Biol Chem.* 1992;**267**(33):23930–6. [PubMed: 1429730].
67. Morfini G, Szebenyi G, Elluru R, Ratner N, Brady ST. Glycogen synthase kinase 3 phosphorylates kinesin light chains and negatively regulates kinesin-based motility. *EMBO J.* 2002;**21**(3):281–93. doi: 10.1093/emboj/21.3.281. [PubMed: 11823421].
68. Morfini G, Pigino G, Szebenyi G, You Y, Pollema S, Brady ST. JNK mediates pathogenic effects of polyglutamine-expanded androgen receptor on fast axonal transport. *Nat Neurosci.* 2006;**9**(7):907–16. doi: 10.1038/nn1717. [PubMed: 16751763].
69. Gordon-Weeks PR. Microtubules and growth cone function. *J Neurobiol.* 2004;**58**(1):70–83. doi: 10.1002/neu.10266. [PubMed: 14598371].
70. Hur EM, Zhou FQ. GSK3 signalling in neural development. *Nat Rev Neurosci.* 2010;**11**(8):539–51. doi: 10.1038/nrn2870. [PubMed: 20648061].
71. Plattner F, Angelo M, Giese KP. The roles of cyclin-dependent kinase 5 and glycogen synthase kinase 3 in tau hyperphosphorylation. *J Biol Chem.* 2006;**281**(35):25457–65. doi: 10.1074/jbc.M603469200. [PubMed: 16803897].
72. Araki Y, Kawano T, Taru H, Saito Y, Wada S, Miyamoto K, et al. The novel cargo Alcadein induces vesicle association of kinesin-1 motor components and activates axonal transport. *EMBO J.* 2007;**26**(6):1475–86. doi: 10.1038/sj.emboj.7601609. [PubMed: 17332754].
73. Hirokawa N. Kinesin and dynein superfamily proteins and the mechanism of organelle transport. *Science.* 1998;**279**(5350):519–26. [PubMed: 9438838].
74. Hirokawa N, Pfister KK, Yorifuji H, Wagner MC, Brady ST, Bloom GS. Submolecular domains of bovine brain kinesin identified by electron microscopy and monoclonal antibody decoration. *Cell.* 1989;**56**(5):867–78. [PubMed: 2522351].
75. Aizawa H, Sekine Y, Takemura R, Zhang Z, Nangaku M, Hirokawa N. Kinesin family in murine central nervous system. *J Cell Biol.* 1992;**119**(5):1287–96. [PubMed: 1447303].
76. Reid E, Kloos M, Ashley-Koch A, Hughes L, Bevan S, Svenson IK, et al. A kinesin heavy chain (KIF5A) mutation in hereditary spastic paraplegia (SPG10). *Am J Hum Genet.* 2002;**71**(5):1189–94. doi: 10.1086/344210. [PubMed: 12355402].
77. Zhao C, Takita J, Tanaka Y, Setou M, Nakagawa T, Takeda S, et al. Charcot-Marie-Tooth disease type 2A caused by mutation in a microtubule motor KIF1Bbeta. *Cell.* 2001;**105**(5):587–97. [PubMed: 11389829].
78. Sabatier MJ, Redmon N, Schwartz G, English AW. Treadmill training promotes axon regeneration in injured peripheral nerves. *Exp Neurol.* 2008;**211**(2):489–93. doi: 10.1016/j.expneurol.2008.02.013. [PubMed: 18420199].
79. Gharakhanlou R, Chadan S, Gardiner P. Increased activity in the form of endurance training increases calcitonin gene-related peptide content in lumbar motoneuron cell bodies and in sciatic nerve in the rat. *Neuroscience.* 1999;**89**(4):1229–39. [PubMed: 10362310].